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PATENT SPECIFICATION

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817,877

Date of filing Complete Specification: Dec. 30, 1957.
Application Date: Jan. 30, 1957. No. 3254/57.
Complete Specification Published: Aug. 6, 1959.

Index at acceptance:—Class 2(3), C1E6K(4:8:9), C3A14C(3:8A).
International Classification:—C07d.

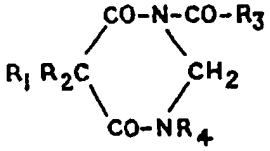
COMPLETE SPECIFICATION

New Pyrimidine Derivatives

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that at patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pyrimidine derivatives and more particularly it relates to certain new pyrimidine derivatives which we have found to possess anticonvulsant properties.

According to the invention we provide in the first place the said new pyrimidine derivatives which are of the formula:—



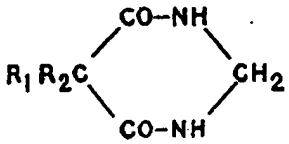
wherein R_1 and R_3 stand for hydrocarbon radicals which may be the same or different and which may optionally be substituted by one or more halogen atoms, R_2 stands for an alkyl radical and R_4 stands for hydrogen or for the group —COR_5 wherein R_5 stands for a hydrocarbon radical which may optionally be substituted by one or more halogen atoms and which may be the same as or different from that represented by R_3.

According to a preferred feature of the invention we provide pyrimidines of the above stated formula wherein R_1 stands for an aryl radical which may optionally be substituted by one or more halogen atoms, or for an alkyl radical, R_2 stands for an alkyl radical, R_3 stands for an alkyl radical which may optionally be substituted by one or more halogen atoms, or for an alkenyl, aryl, aralkyl, or aralkenyl radical and R_4 stands for hydrogen or for the group —COR_5 wherein R_5 stands for an alkyl radical which may optionally be substituted by one or more halogen atoms, or for an alkenyl, aryl, aralkyl, or aralkenyl radical.

According to a still more preferred feature of the invention we provide pyrimidines of the above stated formula wherein R_1 stands for a phenyl radical which may optionally be substituted by one or more halogen atoms, R_2 stands for an alkyl radical, R_3 stands for an alkyl radical which may optionally be substituted by one or more halogen atoms or for a phenyl radical, and R_4 stands for hydrogen or for the group —COR_5 wherein R_5 stands for an alkyl radical which may optionally be substituted by one or more halogen atoms, or for a phenyl radical.

Particularly valuable compounds are 1:3-diacetyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione, 1:3 - dipropionyl-5 - ethyl - 5 - phenylhexahydropyrimidine-4:6 - dione, 1 - benzoyl - 5 - ethyl - 5-phenylhexahydropyrimidine - 4:6 - dione and 1:3 - dibenzoyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione.

According to a further feature of the invention we provide a process for the manufacture of the said new pyrimidine derivatives which comprises acylation of pyrimidine derivatives of the formula:—



wherein R_1 and R_2 have the meaning stated above.

The said acylation may conveniently be brought about by treatment of the said pyrimidine derivatives, preferably under the action of heat, with acylating agents. Suitable acylating agents include for example acid halides, for example benzoyl chloride, and acid anhydrides, for example acetic anhydride, propionic anhydride, butyric anhydride, crotonic an-

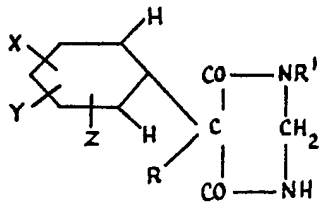
[*Price 3s. 6d.*]

hydride and benzoic anhydride. The reaction may if desired be carried out in a solvent or diluent medium which may be an excess of the acylating agent used. Other solvents for the reaction are inert hydrocarbon solvents, for example xylene. Still other solvents for the reaction are those which have the properties of a solvent and also an acid-acceptor, for example pyridine.

It is to be understood that the process, in the case where R_4 stands for the group COR_5 in which R_5 is different from R_3, may be carried out, if desired, in two stages; acylation to give the mono-acyl derivative followed by acylation with a different acylating agent to give the di-acyl derivative, in which the two acyl groups are different.

As stated above, the compound with which this invention is concerned possess anticonvulsant properties and they are useful in the treatment of epilepsy particularly grand mal epilepsy.

We are aware of U.K. patent specification No. 734,512 in which are described and claimed hexahydropyrimidine - 4:6 - dione derivatives of the formula:—



wherein X and Y stand for hydrogen, halogen or a methyl radical, and Z stands for halogen or a methyl radical, wherein R stands for an alkyl radical or an alkenyl radical of not more than 3 carbon atoms and wherein R^1 stands for hydrogen or for an alkyl radical of not more than 4 carbon atoms.

The invention is illustrated but not limited by the following Examples in which the parts are by weight:—

EXAMPLE 1

75 Parts of 5 -ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione and 200 parts of acetic anhydride are boiled together under reflux for 30 minutes. The mixture is cooled and filtered. The solid residue consists of 1:3-diacetyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione which crystallises from methanol in large colourless prisms of m.p. 125—126° C.

EXAMPLE 2

10 Parts of 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione and 25 parts of propionic anhydride are boiled together under reflux for 30 minutes. The excess propionic anhydride is removed by distillation under reduced pressure, and the residue is washed with petroleum ether (b.p. 40—60° C.). There is obtained 1:3 - dipropionyl - 5-ethyl - 5 - phenylhexahydropyrimidine - 4:6-dione which crystallises from methanol as large colourless prisms, m.p. 95—96° C.

EXAMPLE 3

7 Parts of 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione and 20 parts of *n*-butyric anhydride are heated together at 160° C. for 70 minutes. The mixture is cooled and filtered and the solid residue is washed with petroleum ether (b.p. 40—60° C.) It is then recrystallised from petroleum ether (b.p. 40—60° C.) to give 1:3 - di - *n* - butyryl - 5-ethyl - 5 - phenylhexahydropyrimidine - 4:6-dione as colourless prisms, m.p. 83—84° C.

EXAMPLE 4

8 Parts of 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione and 17 parts of crotonic anhydride are mixed and heated at 160° C. for 1 hour. Crotonic acid and excess crotonic anhydride are removed by distillation under reduced pressure, and the residue is crystallised from methanol. 1:3 - Dicrotonyl-5 - ethyl - 5 - phenylhexahydropyrimidine-4:6 - dione is obtained as colourless prisms, m.p. 91—92° C.

EXAMPLE 5

8.8 Parts of 5 - ethyl - 5 - phenylhexahydropyrimidine 4:6 - dione and 12 parts of benzoyl chloride are heated together at 170° C. for 45 minutes. The mixture is cooled to 60° C., triturated with petroleum ether (b.p. 80—100° C.) and the mixture is filtered. The solid residue is washed with petroleum ether (b.p. 80—100° C.) and is then stirred with cold methanol and the mixture is filtered. The solid residue is then crystallised from methanol and there is obtained 1 - benzoyl - 5 - ethyl-5 - phenylhexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 191—192° C.

EXAMPLE 6

22 Parts of 5 -ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione and 31 parts of phenylacetyl chloride are heated together at 170° C. for 15 minutes. The mixture is then cooled to 100° C., dissolved in petroleum ether (b.p. 80—100° C.) and cooled to room temperature. The solid is filtered off, washed with petroleum ether (b.p. 80—100° C.), stirred with cold methanol and the mixture filtered. The solid residue is then crystallised from methanol and there is obtained 1 - phenylacetyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 133—134° C.

EXAMPLE 7

4.4 Parts of 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione and 6.6 parts of cinnamoyl chloride are heated together at 170° C. for 15 minutes. The mixture is cooled, stirred with hot petroleum ether (b.p. 80—100° C.) and filtered. The solid residue is washed with petroleum ether (b.p. 80—100° C.), stirred with cold methanol and the mixture is filtered. The solid residue is then crys-

tallised from glacial acetic acid and there is obtained 1:3 - dicinnamoyl - 5 - ethyl - 5-phenylhexahydropyrimiden - 4:6 - dione as colourless prisms, m.p. 172—173° C.

EXAMPLE 8

2.2 Parts of 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 -dione and 5.1 parts of chloracetic anhydride are heated together at 145° C. for 30 minutes. Chloracetic acid and excess chloracetic anhydride are removed by distillation under reduced pressure, the residue is stirred with petroleum ether (b.p. 60—80° C.) and the mixture filtered. The solid residue is then washed with petroleum ether (b.p. 60—80° C.), and is then stirred with cold methanol and the mixture is filtered. The solid residue is then crystallised from ethanol and there is obtained 1:3 - di - (chloracetyl) - 5 - ethyl-5 - phenylhexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 149—150° C.

EXAMPLE 9

11 Parts of 5 -ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione and 22.5 parts of benzoic anhydride are heated together at 190° C. for 5 hours. The mixture is cooled, dissolved in an equal volume of hot methanol, cooled, and the solid is filtered off. The filtrate is diluted with water and the mixture filtered. The solid residue is then crystallised from methanol and there is obtained 1:3 - dibenzoyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 149—150° C.

EXAMPLE 10

10 Parts of 5 - (*m* - chlorophenyl) - 5-ethylhexahydropyrimidine - 4:6 - dione and 50 parts of acetic anhydride are boiled together under reflux for 40 minutes. Acetic acid and excess acetic anhydride are removed by distillation under reduced pressure, the residue stirred with petroleum ether (b.p. 40—60° C.) and the mixture is filtered. The solid residue is then crystallised from methanol and there is obtained 1:3 - diacetyl - 5 - (*m* - chlorophenyl) - 5 - ethylhexahydropyrimidine - 4:6-dione as colourless prisms, m.p. 92—93° C.

EXAMPLE 11

1 Part of 5:5 - diethylhexahydropyrimidine-4:6 - dione and 2.5 parts of propionic anhydride are boiled together under reflux for 30 minutes. The excess propionic anhydride is removed by distillation under reduced pressure, the residue is dissolved in petroleum ether (b.p. 40—60° C.) and cooled. The solid residue is recrystallised from petroleum ether (b.p. 40—60° C.) by strong cooling, and there is obtained 5:5 - diethyl - 1:3 - diproprionyl-hexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 69—70° C.

EXAMPLE 12

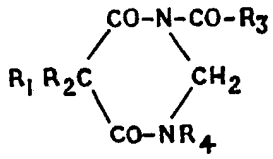
9 Parts of 1 - benzoyl - 5 - ethyl - 5-phenylhexahydropyrimidine - 4:6 - dione are suspended in 90 parts of dry xylene containing 3.15 parts of acetic anhydride, and the mixture boiled under reflux for 45 minutes. The mixture is then cooled, and diluted with petroleum ether (b.p. 40—60° C.). It is then filtered. The filtrate is evaporated to dryness under reduced pressure, the residue stirred with petroleum ether (b.p. 40—60° C.) and the mixture is filtered. The solid residue is then crystallised from methanol and there is obtained 3 - acetyl-1 - benzoyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 129—130° C.

EXAMPLE 13

A mixture of 4.1 parts of acetic anhydride, 2.2 parts of 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione and 10 parts of pyridine is heated at 100° C. for 8 hours, cooled and poured into ice-water. The mixture is allowed to stand for one hour and is then filtered. The solid residue is crystallised from ethanol giving 1:3 - diacetyl - 5 - ethyl - 5-phenylhexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 125—126° C.

WHAT WE CLAIM IS:—

1. New primidine derivatives which are of the formula:



wherein R_1 and R_3 stand for hydrocarbon radicals which may be the same or different and which may optionally be substituted by one or more halogen atoms, R_2 stands for an alkyl radical, and R_4 stands for hydrogen or for the group $—COR_5$ wherein R_5 stands for a hydrocarbon radical which may optionally be substituted by one or more halogen atoms and which may be the same as or different from that represented by R_3.

2. New pyrimidines as claimed in Claim 1 wherein R_1 stands for an aryl radical which may optionally be substituted by one or more halogen atoms, or for an alkyl radical, R_2 stands for an alkyl radical, R_3 stands for an alkyl radical which may optionally be substituted by one or more halogen atoms, or for an alkenyl, aryl, aralkyl or aralkenyl radical and R_4 stands for hydrogen or for the group $—COR_5$ wherein R_5 stands for an alkyl radical which may optionally be substituted by one or more halogen atoms, or for an alkenyl, aryl, aralkyl or aralkenyl radical.

3. New pyrimidines as claimed in Claims 1 and 2 wherein R_1 stands for a phenyl radical which may optionally be substituted by one or more halogen atoms, R_2 stands for an alkyl radical, R_3 stands for an alkyl radical which may optionally be substituted by one or more halogen atoms, or for a phenyl radical, and R_4 stands for hydrogen or for the group $—COR_5$ wherein R_5 stands for an alkyl radical which

may optionally be substituted by one or more halogen atoms, or for a phenyl radical.

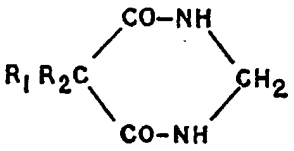
4. 1:3 - Diacetyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione.

5. 1:3 - Dipropionyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione.

6. 1 - Benzoyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione.

7. 1:3 - Dibenzoyl - 5 - ethyl - 5 - phenylhexahydropyrimidine - 4:6 - dione.

8. Process for the manufacture of the pyrimidine derivatives claimed in Claim 1 which comprises acylation of pyrimidine derivatives of the formula:—



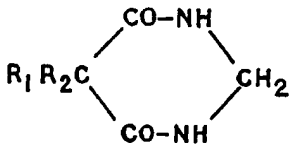
wherein R_1 and R_2 have the meaning stated above.

9. Process as claimed in Claim 8 wherein the acylation is brought about by treatment of the said pyrimidine derivatives with an acylating agent.

10. Process as claimed in Claims 8 and 9 wherein the reaction is carried out under the influence of heat.

11. Process as claimed in Claim 9 wherein the acylating agent is an acid halide or acid anhydride.

12. Process for the manufacture of those of the compounds of Claim 1 wherein R_4 stands for the group —COR_5 in which R_5 is different from R_3, which comprises treatment with an acylating agent of pyrimidine derivatives of the formula:—



wherein R_1 and R_2 have the meaning stated to give the mono - acyl derivative followed by treatment of the mono - acyl derivative so obtained with a different acylating agent.

13. Process as claimed in Claims 8—12 in which the acylation is performed in the presence of a solvent.

14. Process as claimed in Claim 13 in which the solvent is an inert hydrocarbon solvent, for example xylene.

15. Process as claimed in Claim 13 in which the solvent is an acid-acceptor, for example pyridine.

16. The new pyrimidine compounds, claimed in Claim 1, as hereinbefore particularly described and especially with particular reference to the foregoing Examples.

ALFRED O. BALL,
Agent for the Applicants.

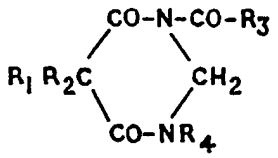
PROVISIONAL SPECIFICATION

New Pyrimidine Derivatives

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare this invention to be described in the following statement:—

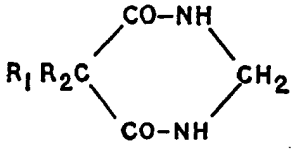
This invention relates to new pyrimidine derivatives and more particularly it relates to certain new pyrimidine derivatives which we have found to show anticonvulsant properties when tested in experimental animals against artificially induced convulsions.

According to the invention we provide in the first place the said new pyrimidine derivatives which are of the formula:—



wherein R_1, R_2 and R_3 stand for hydrocarbon radicals which may be the same or different and which may optionally be substituted, and R_4 stands for hydrogen or for the group —COR_5 wherein R_5 stands for a hydrocarbon radical which may optionally be substituted and which may be the same as or different from that represented by R_3.

According to a further feature of the invention we also provide a process for the manufacture of the said new pyrimidine derivatives which comprises acylation of pyrimidine derivatives of the formula:—



wherein R_1 and R_2 have the meaning stated above.

The said acylation may conveniently be brought about by known means, for example by treatment of the said pyrimidine derivatives, preferably under the action of heat, with acylating agents. Suitable acylating agents in-

clude for example acid halides, for example benzoyl chloride, and acid anhydrides, for example acetic anhydride, propionic anhydride, butyric anhydride and crotonic anhydride. The reaction may if desired be carried out in a suitable solvent or diluent medium which may be an excess of the acylating agent used when that agent is an acid anhydride for example acetic anhydride or propionic anhydride.

The invention is illustrated but not limited by the following Examples in which the parts are by weight:—

EXAMPLE 1

75 Parts of 5 - ethyl - 5 - phenyl hexahydropyrimidine - 4:6 - dione and 200 parts of acetic anhydride are boiled together under reflux for 30 minutes. The mixture is cooled and filtered. The solid residue consists of 1:3-diacetyl - 5 - ethyl - 5 - phenyl hexahydropyrimidine - 4:6 - dione which crystallises from methanol in large colourless prisms of m.p. 125—126° C.

EXAMPLE 2

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EXAMPLE 3

7 Parts of 5 - ethyl - 5 - phenyl hexahydropyrimidine - 4:6 - dione and 20 parts of *n*-butyric anhydride are heated together at 160° C. for 70 minutes. The mixture is cooled and filtered and the solid residue is washed with petroleum ether (b.p. 40—60° C.). It is then recrystallised from petroleum ether (b.p. 40—60° C.) to give 1:3 - di - *n* - butyryl - 5-ethyl - 5 - phenyl hexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 83—84° C.

EXAMPLE 4

8 Parts of 5 - ethyl - 5 - phenyl hexahydropyrimidine - 4:6 - dione and 17 parts of crotonic anhydride are mixed and heated at 160° C. for 1 hour. Crotonic acid and excess crotonic anhydride are removed by distillation under reduced pressure, and the residue is crystallised from methanol. 1:3 - Dicrotonyl-5 - ethyl - 5 - phenyl hexahydropyrimidine-4:6 - dione is obtained as colourless prisms, m.p. 91—92° C.

EXAMPLE 5

8.8 Parts of 5 - ethyl - 5 - phenyl hexahydropyrimidine - 4:6 - dione and 12 parts of benzoyl chloride are heated together at 170° C. for 45 minutes. The mixture is cooled to 60° C., triturated with petroleum either (b.p. 80—100° C.) and the mixture is filtered. The solid residue is washed with petroleum ether (b.p. 80—100° C.) and is then triturated with cold methanol and the mixture filtered. The solid residue is then crystallised from methanol and there is obtained 1 - benzoyl - 5 - ethyl-5 - phenyl hexahydropyrimidine - 4:6 - dione as colourless prisms, m.p. 191—192° C.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1959.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.